☐ 1: Cancer Res. 1992 Nov 1;52(21):6036-44. Related Articles, Links

Targeted therapy of athymic mice bearing GW-39 human colonic cancer micrometastases with 131I-labeled monoclonal antibodies.

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The therapeutic potential of radiolabeled antibodies is usually evaluated in experimental animal models bearing s.c. xenografts. We have established a micrometastatic model of the GW-39 human colonic carcinoma in the nude mouse lung (J. Natl. Cancer Inst., 83: 627-632, 1991) and presented preliminary findings on the efficacy of a 131I-anticarcinoembryonic antigen (CEA) antibody in this model. We now extend our observations on the use of radioiodinated labeled monoclonal antibodies (MAbs) to treat multiple small tumor nodules. Biodistribution and dosimetry analysis was performed for intact and F(ab')2 of NP-4 anti-CEA IgG, Mu-9 anti-colon-specific antigen IgG, isotype-matched irrelevant anti-AFP IgG, and intact MAb 34A anti-lung endothelial IgG antibody. Comparisons were made for rad dose delivered to small s.c. tumors, normal lung, lung with tumor nodules, and isolated tumor nodules. Survival curves were generated for tumor-bearing animals treated 1, 7, or 14 days after tumor cell implantation with these antibodies using the maximal tolerated dose for intact antibodies (275 microCi) and for F(ab')2 fragments (1.2 mCi). The studies established the following observations: (a) in contrast to previous results in a bulky tumor model in hamsters, intact antibodies are more therapeutic than MAb fragments for both NP-4 and Mu-9; (b) tumor nodule size, even on the microscopic level, affects therapeutic outcome; antibodies were more effective when administered 7 days postimplantation (mean nodule diameter, 150 microns) compared with treatment 14 days postimplantation (mean nodule diameter, 750 microns); (c) administration of radioiodinated Mu-9 was exquisitely effective on single avascular tumor cells that had seeded in lung; irrelevant antibody was minimally radiotoxic; (d) as in the bulky disease model, the anti-colon-specific antigen p antibody delivers a higher rad dose than the anti-CEA antibody and is significantly more therapeutic in the micrometastasis model; (e) a higher affinity anti-CEA antibody (MN-14) recognizing the same epitope on CEA as NP-4 was

equally therapeutic; (f) the use of MAb directed against the lung endothelium was not as therapeutic as a tumor-associated antibody; and (g) all tumor-associated antibodies were more efficacious than administration of the maximal tolerated dose of 5-fluorouracil and leucovorin in this human tumor-xenograft model. These results provide further support for the use of radioimmunotherapy in the handling of minimal disease, probably as part of an adjuvant treatment regimen.

PMID: 1394228 [PubMed - indexed for MEDLINE]

1: Viral Immunol. 1996;9(1):35-43.

Induction of antibodies to the bluetongue virus core polypeptide VP7 in sheep by internal image rabbit antiidiotypic antibodies.

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We previously generated rabbit polyclonal antiidiotypic antibody (anti-Id) to a murine monoclonal antibody (M1875) specific for the bluetongue virus core protein VP7, and demonstrated that this anti-Id (designated RAb2-A) had the characteristics of an internal image anti-Id (Ab2 beta). In this communication, RAb2-A was used to induce immune responses in sheep and the responses were compared to immunization with VP7. The immune sera were tested for the presence of anti-VP7 antibodies and the expression of the Id of M1875. Animals immunized with RAb2-A were able to produce M1875-like antibody responses, i.e., they recognized the same or a similar epitope as M1875 and possessed the M1875 Id, without subsequent exposure to the original antigen. This was demonstrated by showing that antibodies induced by RAb2-A (i) reacted specifically with the immunizing anti-Id, (ii) were capable of binding VP7, (iii) inhibited M1875 from binding to VP7, and (iv) inhibited M1875 from binding to RAb2-A. Animals immunized with purified VP7 produced antibodies that possessed the epitope and idiotope specificity of M1875. No antibody responses to VP7 were detected in control animals immunized with either rabbit anti-Id to the pseudorabies virus glycoprotein gII or BHK-21 cell proteins. We conclude that rabbit anti-Id RAb2-A serologically mimics an M1875-defined VP7 epitope sufficiently to function as a surrogate antigen for inducing anti-bluetongue virus VP7 responses.

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1: Cancer Res. 1993 Feb 1;53(3):600-8. Related Articles, Links

Improved radioimmunotherapeutic efficacy of an anticarcinoma monoclonal antibody (131I-CC49) when given in combination with gamma-interferon.

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The moderately differentiated human colon tumor cell line, HT-29, constitutively expresses low levels of the high molecular weight mucin, tumor-associated glycoprotein 72 (TAG-72), and the M(r) 180,000 carcinoembryonic antigen (CEA) when grown as s.c. tumors in athymic mice. We report that the in vivo administration of gamma-interferon (IFN-gamma) resulted in a time- and dose-dependent increase in both TAG-72 and CEA expression in the HT-29 tumors. Immunohistochemical staining revealed a more homogeneous TAG-72-positive tumor cell population after IFN-gamma. Furthermore, both anti-TAG-72 and anti-CEA monoclonal antibodies (MAbs) showed enhanced localization to the HT-29 tumors in mice treated with IFN-gamma. Using that experimental model, subsequent studies presented evidence showing that the combination of IFN-gamma with 131I-CC49, an anti-TAG-72 MAb, resulted in a statistically significant improvement in therapeutic efficacy when compared with 131I-CC49 alone. For example, treatment with 300 microCi of 131I-CC49 initially suppressed HT-29 tumor growth; however, that reduction in tumor growth was transient as evidenced by the emergence of additional tumor growth at later time points. In contrast, an 8-day treatment with IFN-gamma in combination with 300 microCi 131I-CC49 resulted in sustained suppression of HT-29 tumor growth. Thus, IFN-gamma in vivo can substantially increase the TAG-72 expression in human colon tumor xenografts which leads to an increased tumor localization of anti-TAG-72 MAbs and seems to be responsible for the enhanced antitumor effects when IFN-gamma was combined with 131I-CC49. The results provide further evidence for including a biological response modifier, such as IFN-gamma, which can increase the expression of specific tumor antigens (i.e., TAG-72 and CEA) subsequently leading to a dramatic improvement in the antitumor efficacy of a radionuclide-conjugated MAb.

☐ 1: Int J Cancer. 1990 Jul 15;46(1):79-85. Related Articles, Links

Selection of a DTPA chelate conjugate for monoclonal antibody targeting to a human colonic tumor in nude mice.

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Our previous studies with a 90Y-labelled antibody against carcinoembryonic antigen (CEA) conjugated to the cyclic anhydride-DTPA (CA-DTPA) indicated that the accretion of 90Y in the bone may limit the application of 90Y-labelled antibodies for therapy. In this report, we have compared the tumor targeting of CA-DTPA-conjugated antibody to antibody conjugated with 4 isothiocyanatobenzyl (ITC-Bz) derivatives of DTPA in nude mice bearing a human colonic tumor xenograft. In biodistribution studies using an 111In-labelled anti-CEA murine monoclonal antibody (MAb), the CA-DTPA-conjugated MAb showed lower tumor uptake, faster blood clearance, and higher accretion in the liver than any of the 4 ITC-Bz-DTPA-conjugated MAbs. There were smaller differences among the 4 ITC-Bz-DTPA conjugates. Whole-body autoradiography of animals given 90Y-MAb prepared with the CA-DTPA or the ITC-Bz-DTPA showed less radioactivity in the bone with the ITC-Bz-DTPA-MAb than the CA-DTPA-MAb. 90Y uptake in the bone corresponded with regions of low proliferative activity as defined by 3H-labelled thymidine, suggesting that the 90Y was in the cortex rather than the marrow. These studies clearly show an advantage of the ITC-Bz-DTPA derivatives for 90Y and 111In labelling of MAbs.

PMID: 2114375 [PubMed - indexed for MEDLINE]

☐ 1: Cancer Immunol Immunother. 1987;24(3):202-6. Related Articles, Links

Comparison of multiple anti-CEA immunotoxins active against human adenocarcinoma cells.

Levin LV, Griffin TW, Childs LR, Davis S, Haagensen DE Jr.

Anti-carcinoembryonic antigen (CEA) immunotoxins constructed with multiple anti-CEA antibodies (goat and baboon polyclonal, and three murine monoclonal antibodies) by covalently linking them to the A chain of ricin via a disulfide bond all function as potent and specific toxins for CEA-bearing cells, suggesting that the CEA molecule is capable of directing productive internalization of ricin A chain. The high potency of anti-CEA immunotoxins apparently makes addition of ricin B chain unnecessary for high toxic efficiency, as in some other systems, because presence of the B chain reduces target cell specificity. Several characteristics of the immunotoxins which might account for their cytotoxic potency were studied. Equilibrium association constants of the goat, baboon, and murine monoclonal C-19 antibodies with fluid-phase CEA were determined by using Langmuir plots and were found to be 8.79, 6.61, and 8.13 X 10(9) M-1, respectively, indicating the high and similar affinities of the three antibodies toward CEA. Radioimmunoassay binding studies of the three immunotoxins with 125I-CEA showed that the antibody portions of the molecules retained the ability to form complexes with CEA after conjugation to ricin A chain. The maximum number of anti-CEA antibody molecules bound per cell, as demonstrated by 111In-labeled C-19 binding assays with CEA-bearing cell lines, varied from 2.65 X 10(5) per cell for HT29 to 2.01 X 10(6) for LoVo, with an intermediate value of 1.17 X 10(6) per cell for WiDr. Cytotoxicity of the immunotoxins was assessed by inhibition of protein synthesis and expressed as a median inhibitory dose (ID50). Comparison of the ID50's of each immunotoxin on the three cell lines has shown that the immunotoxin made of the monoclonal C-19 antibody is in general 6 to 7 times more cytotoxic than the goat and baboon antibody immunotoxins. The affinity of CEA-antibody binding is probably an important, but not a sole factor in determining the immunotoxin potency. The fact that the antibodies with very similar affinity toward fluid phase CEA make immunotoxins of different potency might indicate that interactions with membrane-bound CEA are more complex and/or the efficiency of internalization of various immunotoxins is different. An important factor in immunotoxin action appears to be the CEA content in

target adenocarcinoma cells.

PMID: 3496151 [PubMed - indexed for MEDLINE]

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1: Mol Immunol 1995 Oct;32(14-15):1157-69 Related Articles, Links

Molecular cloning and characterization of human thyroid peroxidase autoantibodies of lambda light chain type.

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IgG class thyroid peroxidase (TPO) autoantibodies with kappa light (L) chains predominate in serum and the genes for a large repertoire of such autoantibodies have been characterized. The present study was performed to clone and characterize TPO autoantibodies with lambda L chains which comprise approximately 20% of serum TPO autoantibodies. From a combinatorial IgG H/lambda L chain cDNA library in the phage display vector pComb3, 24 TPO-binding clones with lambda L chains were isolated, comprising three different heavy (H) and light (L) chain combinations. These combinations utilized two genes from the Vlambda II and IIIb families (closest germline genes DPL11 and hsigg11150) and three genes from the VH1, VH3 and VH4 families (VH26, 4.34 and hv1L1). The deduced amino acid sequences of these H chains were quite different from those of kappa F(ab) isolated using the same H chain library. We expressed the proteins for these three lambda F(ab), as well as for a lambda F(ab) (Humlv318 L chain/DP10-like H chain) previously isolated from another patient. The affinities for TPO of the lambda F(ab) (Kd 8 x 10(-10) M to 10(-7) M) were lower than those of the kappa F(ab) (Kd approximately 10(-10) M). For two lambda F(ab), both H and L chain genes were close to germline configuration, but there was no straightforward relationship between the extent of somatic mutation from germline configuration and affinity for TPO. All four lambda F(ab) bound less well to denatured TPO as to native TPO. The three F(ab) for which sufficient protein could be expressed for competition studies all recognized domain B within the immunodominant region on TPO previously identified using F(ab) with kappa L chains. Aside from these TPO-specific F(ab), only a few other human IgG class, organ-specific autoantibodies with lambda L chains have been characterized at the molecular level. Our study significantly augments the small database on this category of autoantibodies in general.

PMID: 8544864 [PubMed - indexed for MEDLINE]

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